Pharmaceutical Hydrates: Prevalence, Properties and Progress

by

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Dedication

To my late grandmother, Edna Zunic. Thank you for raising the woman who raised me to be the best I can be. I hope you are proud of me and I miss you.

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Table of Contents

List of Figures

List of Tables

List of Appendices

Abstract

Among pharmaceutical solids, hydrates are a commonly chosen crystalline form for commercialization. Compared to their anhydrous counterparts, hydrates are often more stable due to strong hydrogen bonding networks between water and pharmaceutical molecules. However, this stability atypically comes with the tradeoff of lower solubility, and research is needed to uncover novel pharmaceutical forms displaying both optimal solubility and stability. This dissertation focuses on both common and unconventional methods of hydrate crystal modification in order better understand limitations of current approaches in the field as well as chart promising directions for future research.

Polymorphism, the ability of a molecule to pack into multiple crystal forms, can result in forms with unique physical and chemical properties. Extensive analysis of crystal forms published in the Cambridge Structural Database, however, alludes to an observed low prevalence of hydrate polymorphism among known structures, indicating this route is not ideal for hydrate modification. Other methods, such as precise control of water available during crystallization, can also have an effect on the crystal form achieved. With the antileukemia compound mercaptopurine, this method results in the discovery of a hemihydrate crystal form, which displays superior solubility and bioavailability compared to the commercially used monohydrate form. The hemihydrate form also displays the highest known dehydration temperature for a non-salt organic molecule reported in the literature (240 °C). Extensive material characterization explains the physical basis for these properties, with the hemihydrate water molecules residing in electrostatically shielded pockets within the structure.

Controlling water present during crystallization of miconazole also allowed for the discovery of a novel hemi(hydrogen peroxide) solvate form. Characterization such as thermogravimetric analysis, Karl Fisher titration, and ^{31}P NMR verify the presence of hydrogen peroxide within the structure and X-ray diffraction shows the similar but not isostructural packing of the solvate in comparison to the known hemihydrate form. Solid form antifungal

susceptibility methods are under development to test the efficacy of this hydrogen peroxide solvate in comparison to the other known solid forms of miconazole.

Chapter 1

Introduction

1.1 Pharmaceutical Solids

Active Pharmaceutical Ingredients (APIs) are the bioactive components of a drug, which, when combined with stabilizers and fillers called excipients, produce the medicines familiar to many.[1] While medicinal compounds have been used in some context since at least 1100 BCE, modern pharmaceutics did not take off until World War II caused a need for an increase in research and development of new antibiotics and pain relievers as well as medicines for other conditions.[2] Overall, many chemical entities may be considered pharmaceuticals, including those not initially discovered or marketed as such; nitroglycerine and warfarin were initially used as an explosive and rat poison, respectively.[2] However, the modern pharmaceutical industry, after the creation of the Food and Drug Act in 1906, has seen 1,453 new molecular entities between its start and the end of 2013.[3] These species are now accepted and maintained by the U.S. Food and Drug Administration (FDA), which holds strict requirements on the appropriate qualifications and screening an entity must undergo before approval.[4,5]

The study of pharmaceutical sciences is composed of many different categories, including drug design and analysis, drug action and behavior, and formulations and delivery, all of which have a common goal of discovering a novel API for commercialization.[6,7] Drug design often begins with a target and a screen for molecules effective against that target.[2] Rational design can be used to modify the molecule until toxicity and efficacy are balanced. Finally, formulations are developed to best deliver the dose required, and this is most often in the form of a solid, whether as a tablet, capsule, or suspension. Solids are the most common dosage form for several reasons.[7] Shelf stability is an important property of any pharmaceutical, and where liquids are more likely to change concentration or degrade over time, stable solids will retain their efficacy for years. Administration as solids is also preferred, for control of a dose compared

to measuring out a liquid, and ease of transportation and storage without the risk of spills or contamination.[7] The work of a solid-state scientist is complex, as properties of the solids will cross into many areas of the pharmaceutical industry (Figure 1.1).[8] The initial goal for a solid-state chemist in this field is to modify crystallization or precipitation conditions in order to fully characterize all the available solid forms of a molecule for the goal of optimal solubility and bioavailability in the body,[8] a procedure now required by the FDA.[4,5]

The two broad classes of solids that are generally accepted include crystalline and amorphous materials,[5,6] where crystalline materials may be broken down into many more subclasses (Figure 1.2). Amorphous materials lack any long-range order, and are ideally preferred for pharmaceuticals due to their increased solubility. However, the lack of long range order is often a kinetically preferred state, and the drive for crystallization makes these forms one of the most unstable type of solids.[8] Crystalline materials, therefore, are preferred for commercialization because their thermodynamic stability provides a reliable set of physical properties for the basis of a dosage form. The choice of which crystalline form is used, however, can be a complex matter.[7]

1.2 Crystalline Properties

Anhydrates are the most common type of crystalline material, but are not always the preferred choice for pharmaceuticals. Anhydrate forms are often susceptible to absorption of water under humid conditions,[9] which can cause a change in form during storage. Other options include multicomponent systems, such as hydrates or solvates, salts, and cocrystals. Salts are also preferable for pharmaceuticals due to the increased solubility of ionic systems in water, and their increased thermal stability.[7] These too, are susceptible to high humidities however, and may become less soluble if water is absorbed into the crystal structure. Hydrates are very common in pharmaceuticals, due to the ubiquity of water in the environment, as well as their stability to variable humidity conditions, but suffer from a lower solubility in the body.[10] Hydrates often form because water allows for better packing efficiency of molecules to form crystals,[11] and therefore, since the molecules are interacting with water in the solid state, the system has less of a drive to dissolve and interact with water in a solution phase. This is different from all other solvates, where the water solubility is often higher, but so is the toxicity, and therefore very few pharmaceuticals are marketed today as any form of organic solvate. Cocrystals, finally, are

composed of two neutral solid components, and have emerged in the last few decades as a highly modular class of crystalline materials which can be tuned to control specific physical properties based on intermolecular interactions in the solid state.[12]

The properties controlled by the solid state can range from melting point, to vibrational modes, to dissolution rate (Figure 1.3).[13] All of these properties will be controlled by the intra- and intermolecular interactions in the solids,[14] with the more stable solids usually containing stronger electrostatic or hydrogen bonds and the kinetically metastable forms containing weaker bonds which are easier to break. Most of these physical properties can be measured with various forms of spectroscopy, such as Raman or Infrared, as well as thermal analyses such as Differential Scanning Calorimetry (DSC) or Thermogravimetric Analysis (TGA).[15,16] It is essential, especially for pharmaceuticals, to understand all possible phase transitions from changes in temperature, as well as decomposition and melting points of any crystal forms to understand the range of storage conditions a final dosage can withstand.

For pharmaceuticals, dissolution rate and solubility are some of the most important physical properties,[17,18] and metastable forms tend to show an increased dissolution rate. As with amorphous forms, if the metastable form is *too* unstable, it could potentially convert to the more stable form under certain storage conditions, negating its use. Therefore, a proper balance between stability and solubility must be achieved when choosing a solid form for commercialization.

The other important characteristic of pharmaceutical molecules is intestinal permeability, which combines with solubility to predict the bioavailability of the drug in the body. Amidon and coworkers developed the Biopharmaceutics Classification System in the early 1990s to classify pharmaceuticals based on their water solubility and intestinal permeability (Figure 1.4),[18] and the FDA has adopted this system in their guidance for new and abbreviated drug applications.[19] In most cases, the permeability of a molecule is determined by the molecular structure of the molecule itself, and does not rely on the solid form the molecule dissolved from. Hydrophobic molecules, while having lower water solubility, are more likely to permeate the lipophilic intestinal membranes, while hydrophilic molecules are exactly the opposite. It has been shown that through the inclusion of certain excipients in a dosage form, both the solubility and permeability of a molecule can be affected;[20-24] however, this modulation is often in the direction

of increased solubility through complexation, which has a detrimental effect on the permeability. Recently in the literature, researchers have begun considering the permeability of cocrystals,[25-30] and have noticed increased permeability of dissolved cocrystals over that of physical mixtures, indicating that some type of physical interaction is carried into solution from the solid that provides a benefit for permeability.

1.3 Polymorphism

Polymorphism in pharmaceutical crystals is very common, and results when two or more crystalline structures exist that contain the same molecular entities that are arranged differently in the solid state (Figure 1.5).[31] All crystal types can form polymorphs, whether single component anhydrates or any form of multicomponent system, and isolation of polymorphs can greatly depend on the conditions used for crystallization.[32] Polymorphism has been known since the early 1800's, but has never garnered a comprehensive definition agreed upon by all crystal engineers.[33] This ambiguity has resulted in many different methods for analysis of polymorphism and its prevalence,[34-37] leaving researchers with an unknown propensity for how common polymorphism is in general.

One feature of polymorphic compounds that is widely agreed upon is the effect that polymorphic forms can have on the physical properties of a compound. Rearrangement of molecular packing in a crystal structure can have a drastic effect on properties,[14] just as with changes in crystal type. For pharmaceuticals in particular, it is known that changes in polymorphic forms will have an effect on the solubility and dissolution rate of the solids.[7] As mentioned above, higher solubility is desired for pharmaceuticals, as long as it is not at the expense of the stability of the form. One of the most recognizable cases where polymorphism affected a marketed pharmaceutical is with the medication Ritonavir.[38] When the initial solid was marketed, there was only one polymorphic form known and therefore commercialized. However, after two years on the market, a more stable form II was observed in capsules which greatly lowered the oral bioavailability of the drug. The medication had to be temporarily removed from the market until this problem could be averted, and highlighted for the community the importance of a full polymorph screen of pharmaceuticals before entrance to the market.

When considering organic compounds, most molecules that display polymorphism only have two structurally characterized forms to date, but there are a few examples of remarkable,

highly polymorphic compounds (Figure 1.6). In 2012, the non-steroidal anti-inflammatory drug (NSAID) flufenamic acid was shown to display nine different polymorphic forms, with eight of these being structurally characterized after growth on polymer surfaces.[39] In 2014, it was determined that the antidepressant drug aripiprazole also had eight of its ten known polymorphic forms structurally characterized, with the last being due to a low temperature phase transition from form II.[40] While polymorphic prediction is still a growing area, it is important to understand that while all compounds may have the potential to exhibit polymorphism, crystallization screening and molecular structure may play significant roles in the frequency that polymorphism is experimentally observed.

1.4 Crystalline Hydrates

There are necessary distinctions when discussing crystal types in order to separate out cocrystals (comprised of two neutral, solid components) and solvates (comprised of one solid and one liquid component).[41,42] While cocrystals are a newer class of crystalline materials, organic solvents have been commonly used in crystallization conditions in the past, and depending on the method of crystal growth, solvent molecules may get trapped in the lattice, or even contribute to the stability of a growing structure to produce a solvated crystal., The most commonly observed solvates are hydrates, where the solvent is water.[10,13] Hydrates are observed more frequently than organic solvates, but not just because water is used commonly as a crystallization solvent. Many solid forms are also susceptible to absorption of water and may convert to hydrates upon storage.[37] Due to the abundance of water in the environment, water may also absorb into an organic solvent, and get preferentially incorporated into a structure, as the vast array of possible hydrogen bonding motifs with water molecules allows for stabilization of many molecules into crystalline solids.[43]

While organic solvates are not common for pharmaceuticals due to toxicity issues, hydrates are very commonly administered as a marketed form. Since stability is highly desired in crystalline solids, hydrates are often optimal due to their strong hydrogen bonding networks, allowing for lower energy structures. However, water incorporated into the solid structure typically reduces the water solubility of the form, the other critical factor for pharmaceuticals.[10,37] While a balance between solubility and stability is optimal, the preferred form for a marketed pharmaceutical will consist of a hydrate if the anhydrous form is too

unstable, as any conversion once tableted will result in an inconsistent dosage of medication. Therefore, novel methods of crystal growth and screening are necessary in order to accelerate the discovery of stable crystal forms for marketing, whether those still contain water in some fashion or another chemical in its place.

1.5 Organization of thesis

This thesis focuses on the modification of crystalline hydrate pharmaceuticals in order to increase their dissolution, solubility, and bioavailability. In Chapter 2, the prevalence of organic polymorphic compounds in the Cambridge Structural Database[44] is assessed in order to determine the propensity for hydrates to display polymorphism. Despite their abundance, hydrates display one of the lowest percentages of polymorphism among all crystal types. Therefore, we have determined other methods of crystallization modification are preferred in order to find novel crystal forms of hydrate forming pharmaceuticals.

Chapter 3 describes the discovery of a novel hemihydrate form of the antileukemia drug, mercaptopurine, originally discovered in the 1950's.[45] Crystals of this novel form not only exceed the solubility of the commercially used form, but show ~3× the bioavailability of the marketed monohydrate. The hemihydrate also shows the highest dehydration temperature of any known neutral organic hydrate.[46-50] Chapter 4 extends this work with a comprehensive analysis to understand the physical route for these improved physical features. It was found that empty pockets in the anhydrate structure are able to be filled with water under controlled conditions to produce the hemihydrate form, giving a structure which shows optimal solubility as well as thermal and shelf stability.

Chapter 5 explores a new solid form discovery method by replacing the water in a hemihydrate form of the antifungal medication miconazole, with structurally similar hydrogen peroxide. This method is viable for the use of a topical medication in order to increase the antifungal and antibacterial properties of miconazole with a stable peroxide solvate.

1.6 Figures

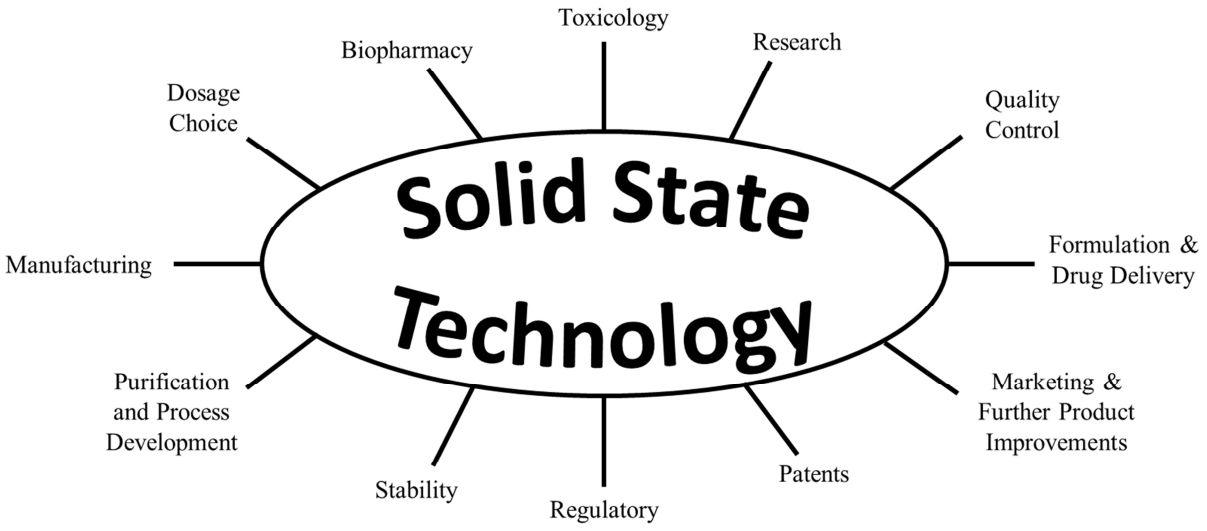

Figure 1.1. An illustration of fields of the pharmaceutical industry impacted by solid-state chemistry (adapted from Byrn et. al., *Solid-State Chemistry of Drugs*).[14]

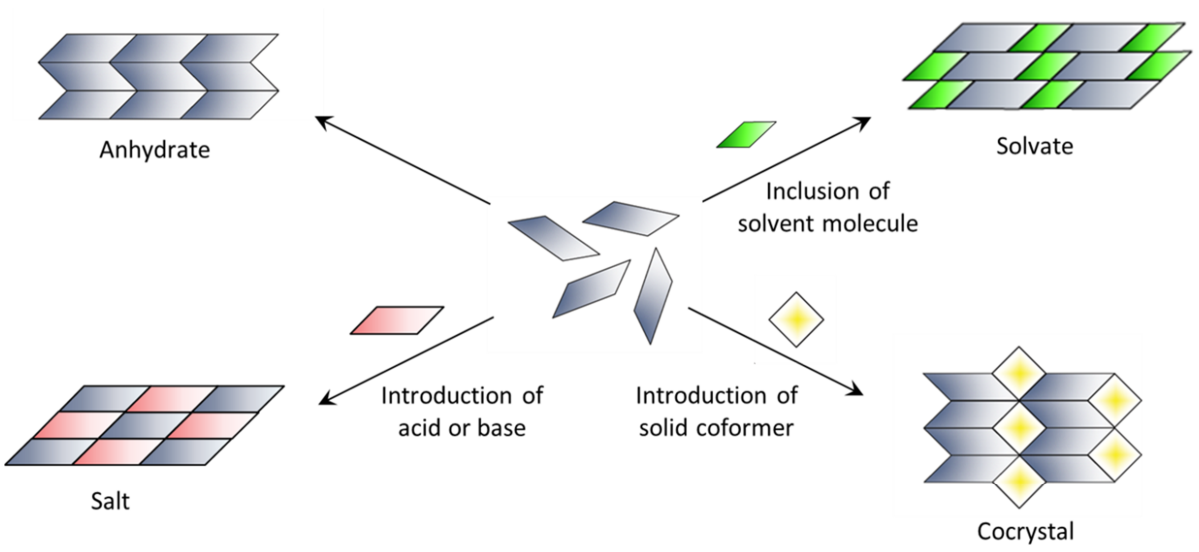

Figure 1.2. Diagram of the subclasses of crystalline materials.

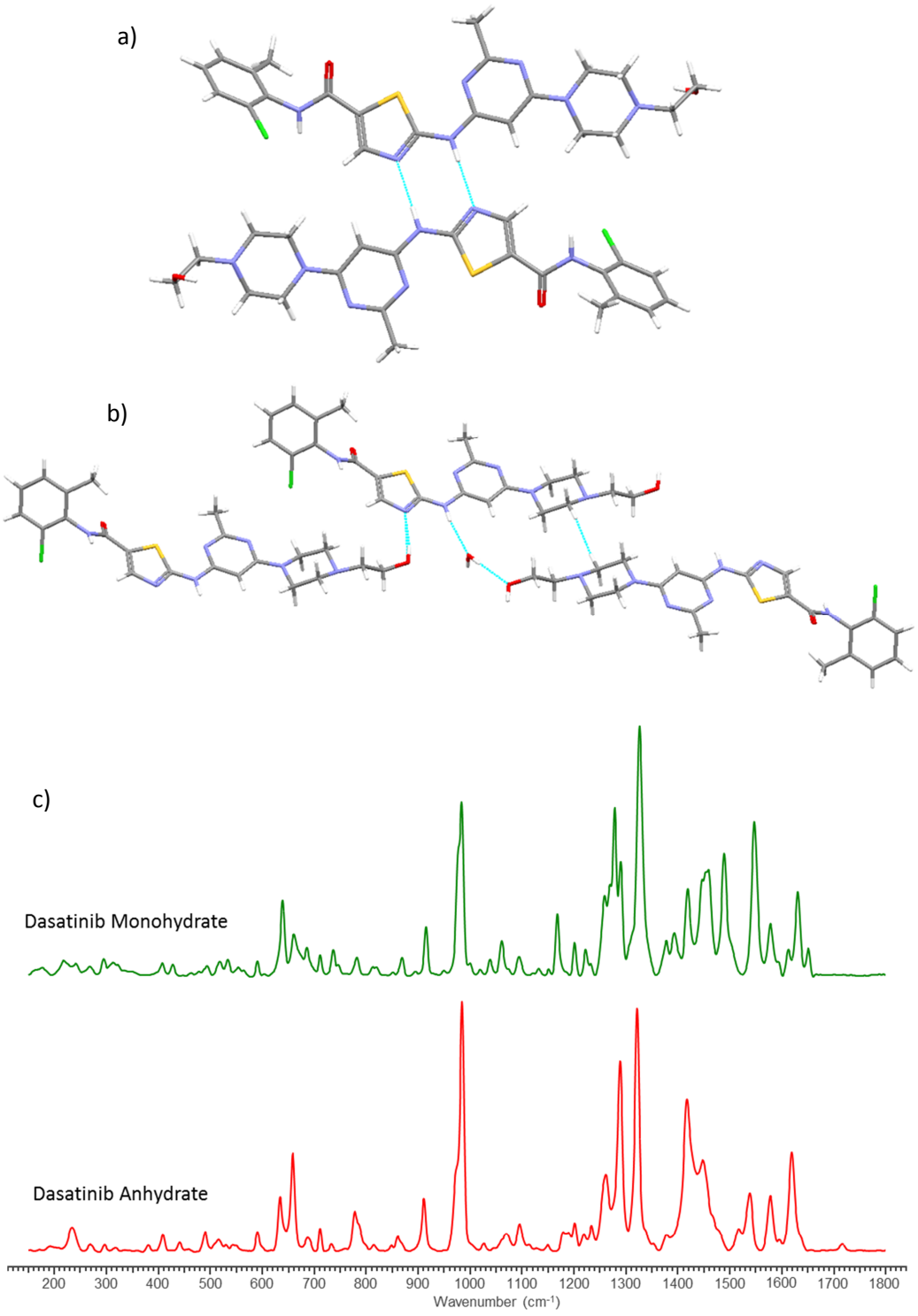

Figure 1.3. (a) Hydrogen bonding of dasatinib anhydrate molecules. A homodimer is formed with N···HN bonding. (b) Hydrogen bonding of dasatinib monohydrate molecules with water. The homodimer is broken up by the presence of a water molecule. (c) Raman spectra of the two forms of dasatinib illustrating the difference in vibrational modes of the two structures.

Biopharmaceutics Classification System

Solubility / Permeability	High	Low
High	Class I	Class II
Low	Class III	Class IV

Figure 1.4. Chart showing solubility and permeability qualifications for the four classes in the Biopharmaceutics Classification System.

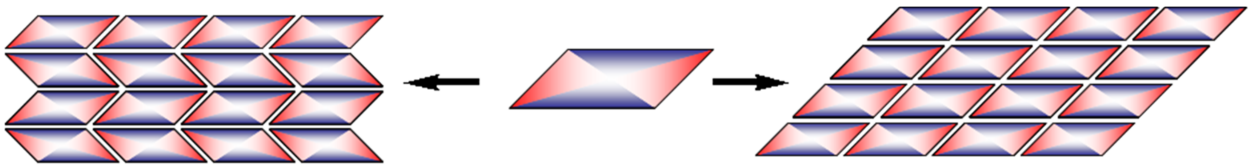

Figure 1.5. Illustration of how one molecule can pack into multiple structures known as polymorphs.

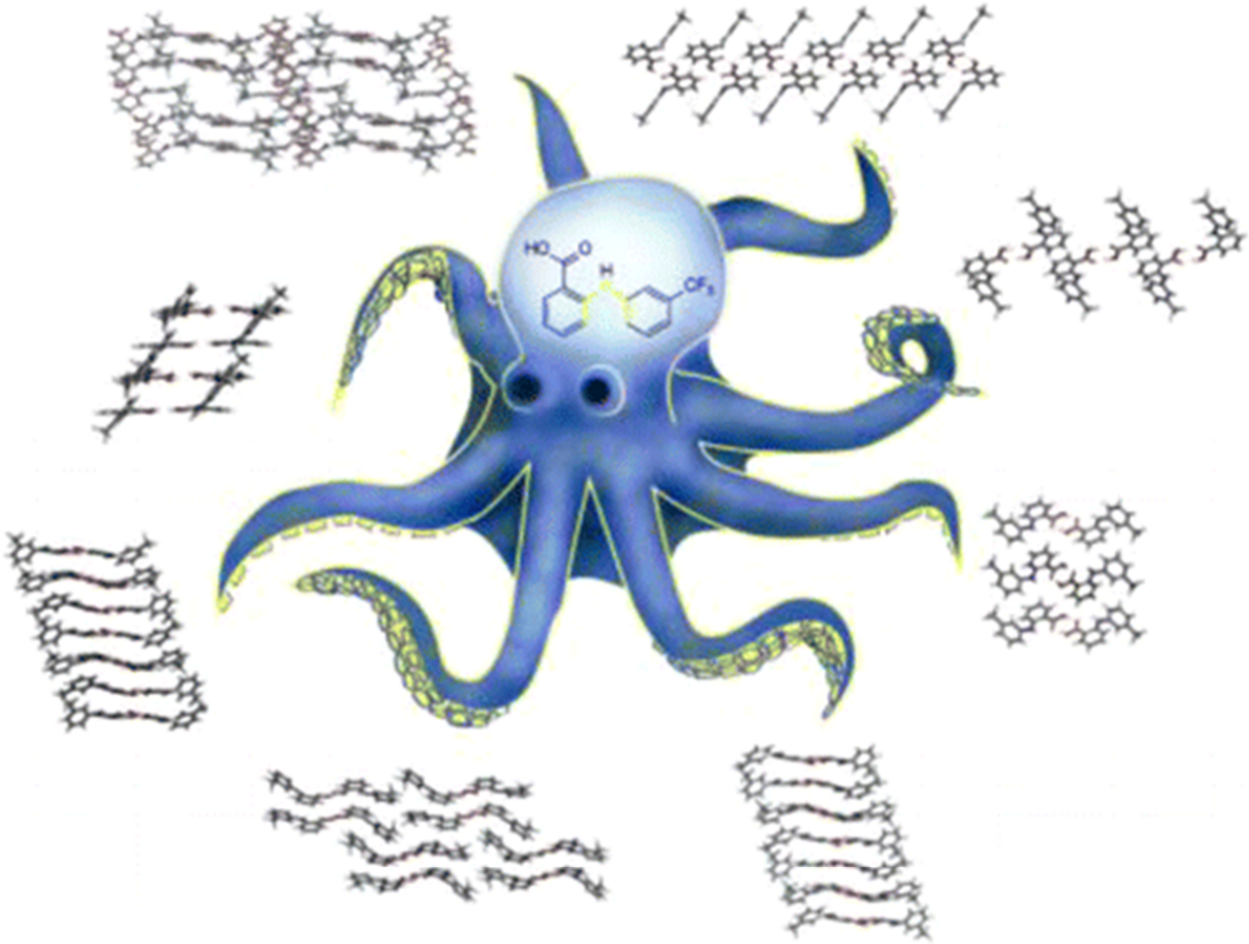

Figure 1.6. Crystal structure displays of the eight structurally characterized forms of flufenamic acid.[39]

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Chapter 2

Survey and Analysis of Crystal Polymorphism in Organic Structures[†]

2.1. Introduction

Polymorphism is a concept that has been well known within the crystallization field since Mitscherlich discovered different crystal forms of the same phosphate salt in the early 1800's.[1] However, it was not until the late 1960's that McCrone presented a review on the relevance of this concept in the field of pharmaceuticals, where it would eventually become one of the most studied topics in solid-state organic chemistry.[2] McCrone famously posited that the discovery of polymorphs is correlated with the energy and time put into researching a compound.[2] We have spent the last 15 years in our lab researching crystallization and polymorphism[3,4] and indeed, polymorphs of many molecules have been isolated in this time,[5-9] leading to advancements in the understanding of solid-state molecular packing and how variations in packing can affect physical properties. We are also not alone in this endeavor; a search for the term "polymorph" in the journal Crystal Growth & Design shows that on average, 18% of the research articles and communications published in the last 15 years contain this term (Table B.1).[a] However, funds are limited and researcher time is in high demand and so scrutinizing every new organic molecule for polymorphism is not a realistic goal. With this obvious constraint, it is important to understand the limitations of this research topic and how to utilize what has been previously discovered in order to direct future research most efficiently.[10] Herein we examine organic polymorphs deposited in the Cambridge Structural Database (CSD) to determine the trends in prevalence as a function of time and crystal type providing an overview of research activity and progress in the field.

[†] Unpublished work.

[a] Searching for this term in Crystal Growth & Design leads to very few false hits involving genetic polymorphism or indeed other meanings of the term. See Experimental Methods for more details.

The CSD is the most extensive and accessible listing of crystal structures within the scientific community, and it serves as the basis for the analysis herein.[11] Using this approach will underestimate the occurrence of a phenomenon such as polymorphism because many crystalline materials are not crystallographically characterized and deposited into this database. For example, Stahly showed that solid form screening can lead to many polymorphic forms being discovered, albeit for a subset of pharmaceutically relevant compounds whose structures were not disclosed.[12] In order to choose a more inclusive subset of crystals, the entries available in the CSD are analyzed here to make general conclusions based on the relative occurrence of polymorphism in organic compounds.

When a structure is deposited in the CSD, information about the compound is recorded such as unit cell parameters, molecular makeup, and the experimental conditions used to solve the structure. This can also include other relevant data tags such as the mention of polymorphism of the specific chemical entity. However, since the term polymorphism is not always uniformly defined, entries are sometimes flagged as polymorphs that are not equivalent in nature.[1, 13-15] In addition, there is a lack of distinction between structures that represent two forms that can coexist under the same conditions, and those solid phases of a compound existing only under specific and separate conditions. Practically, this relationship is important because the stability of a form directly relates to its properties, such as bioavailability in pharmaceuticals or performance in energetic materials.[16-20] For this reason, attempts are made herein to distinguish between these types of polymorphs in the CSD.

Building on past efforts involving surveys of subsets of the CSD,[1,10,21,22] we sought here to be more comprehensive and inclusive in this analysis such that a number of trends can be discerned; these trends may be considered as one piece of the puzzle that is crystal polymorphism. Sarma and Desiraju conducted a seminal study of polymorphism prevalence, where both organic and organometallic single component polymorphs from the CSD were analyzed based on carbon content and molecular flexibility.[22] Overall, they concluded polymorphism to be "essentially a random phenomenon" with molecules of all sizes showing the same prevalence for polymorphism at ~3%.[22] Cruz-Cabeza et al. analyzed a subset of the 2011 CSD as well as internal statistics from solid form screens performed at Roche and Eli Lilly for the occurrence of polymorphism, and found again that molecular flexibility and size were not

correlated with polymorphism, but that "each compound constitutes a new challenge" when understanding the phenomenon.[10] Through the years, others have also compiled data from internal sources or pharmaceutical databases, such as the European Pharmacopoeia or the Merck Index but such analyses naturally are biased towards pharmaceutical systems which have been screened specifically for polymorphism.[12,23] To determine the relative propensity for any organic crystal type to display polymorphism, the present study analyzes all organic structures in the 2015 CSD with 3D coordinates known. Making these results available to scientists interested in crystallization for any purpose, beyond just pharmaceuticals, will help to inform all about the relative likelihood of encountering polymorphs of a particular crystal type based on past research efforts.

2.2 Results and Discussion

Figure 2.1 shows that most (75%) of the entries on the list of 4,573 unique polymorphic refcodes (Table B.2) identified in the Experimental Methods were confirmed as polymorphic compounds (Table B.3). There were, however, a large percentage of compounds with only one crystal form characterized (details in Tables B.4 and B.5). In light of van de Streek and Motherwell's 2005 assessment of polymorphic compounds in the CSD,[21] we were surprised by the number of cases with only one crystal form present and analyzed these instances further. Slightly more than 55% of these refcodes do in fact have only one presence in the CSD. In these cases, the compounds were most likely flagged as polymorphic due to their associated publications mentioning this concept when a second form may have only been characterized by a method other than crystallography.[24,25] The remaining hits were found to have other entries present in the CSD, albeit only by removing the search parameter of having 3D coordinates available. This parameter has been chosen in order to only select those compounds with full structural proof of polymorphism, and thus these 347 entries are excluded in the overall. However, in the remaining few cases where multiple entries were listed with 3D coordinates known, they show up on this list because only one entry was flagged as a polymorph. The reason some of these polymorphic entries are not flagged upon deposition of the structures in the CSD is unknown, but these 61 compounds have been included in the overall list as they do in fact

display polymorphism.[b] The small list of entries in the Other category, which have also been excluded from the overall list, is shown in Table B.6.

When analyzing organic crystalline materials, characterization of physical properties, such as solubility or melting, for example, is especially crucial for polymorphs.[14,26,27] Property measurements should be conducted under comparable conditions, without changes in temperature or pressure, to make concrete conclusions about polymorphic differences. It was observed that a small group (~10%) of the organic polymorphic compounds were a result of changes in structure due to temperature or pressure (Figure 2.1). Due to the complications with assessing physical properties of these polymorphs for comparison under the same conditions, we have separated these (termed here as Class B) from the rest of the polymorphs (Class A) to show the occurrence of this type of polymorphism (see Experimental Methods for details on determination of class B polymorphs). However, both classes are included in the comprehensive list. The overall list of polymorphic compounds (Table B.3) was broken down further into crystal types (single component anhydrates, salts, hydrates, non-hydrated solvates, and cocrystals) as shown in Figure 2.1. As expected, anhydrates are the most common crystal type of polymorphic compound, with salts as a distant second. For Class B, the salt category is much larger, at 32%, than for Class A (14%). In salts, the addition of coulombic attraction/repulsion on top of other noncovalent interactions is a differentiating feature. Perhaps, the weaker distance dependence of ionic interactions overlaid with interactions much more sensitive to intermolecular distance leads to a far greater prevalence of temperature-dependent phase transitions in salts during changes in lattice constants.

To further put the listing of polymorphs into context, the overall occurrence of each type of organic crystal was analyzed to compare the number of polymorphic compounds relative to the number of organic compounds in general (Figure 2.2). Comparison of the number of polymorphic compounds with those considered to be monomorphic in the CSD (only having one crystal form characterized) provides a good indication of the relative occurrence of polymorphism in each crystal type. While some crystal types are obvious to search for, such as anhydrates (one chemical unit), or salts (containing ions), most multicomponent systems are more complicated. As per majority opinion of a group of crystal engineering researchers in 2012,

[b] Three compounds have polymorphic forms of both H and D species, which extends the list to 4,576 unique chemical systems.

we have chosen in this study to separate hydrates, solvates, salts, and cocrystals as separate multicomponent systems.[28] Since there is no qualifier in the CSD to search for solid or liquid components, all entries containing two or more chemical units had to be individually examined to separate those that contain at least two neutral solid components (at 25 °C and 1 atm) for cocrystals from all solvated entries. Starting with all organic entries in the CSD with 3D coordinates known, the data are then divided into single component anhydrates and each form of multicomponent system. Each search can be further examined to provide the total number of refcode families (see Experimental Methods for details) in order to show the number of unique compounds in each area. Similar searches were also conducted adding the tag "polymorph". Finally, the previous analysis of the number of polymorphic compounds in each crystal type is included. For the multicomponent systems, this is also further broken down into subtypes of each group, in order to show the propensity of each subtype in reference to its crystal type. According to the nomenclature of Grothe et. al., "true" crystals of a crystal type refer to structures, for example, containing only two ions of a salt or only one compound with water for a hydrate.[29]

One area of note is that among multicomponent systems, the true crystal forms are the most prevalent for polymorphism in all cases except hydrates, where salt hydrates dominate. Ionic systems often display high propensities towards moisture sorption, most likely leading to the higher occurrence of salt hydrates than true hydrates. This phenomenon of true crystal prevalence was investigated further to determine if the occurrence of crystals with >2 chemical components is low for all organics, beyond just polymorphs, but the data do not support this suggestion. In fact, over 24,000 unique structures of crystal systems with 3+ components have been structurally characterized. Due to the recent focus in literature on cocrystal polymorphism,[30-32] these data highlight an attractive area for further study in the future to discern if there is a physical basis for the low occurrence of polymorphism in systems with more than two components.

The overall percentages of polymorphism for each crystal type were calculated by dividing the number of polymorphic compounds by the total organic compounds for that crystal type (yellow highlighted values in Figure 2.2). These data give a static picture for 2015, compared to other values presented in the past, and show that cocrystals (1.58%), salts (1.36%), and anhydrates (1.22%) all display approximately the same percentage of polymorphs, whereas

hydrates and other, non-hydrated solvates yield polymorphs with lower incidence (0.63 and 0.42%, respectively). These percentages can and have changed over time. For hydrates, the low incidence is surprising given the ubiquity of water, but for solvates, the origin of the low incidence is more readily understood. Solvates are often not sought after, and frequently occur as an incidental result of a crystallization, such that searching for additional polymorphs is not commonly carried out. The above analysis regarding percentages of polymorphism for each crystal type shows that, as of 2015, cocrystals have a higher propensity for polymorphism than single components among structurally characterized compounds thus resolving a debate that has lingered for some time.[10,33] Due to the small difference in these percentages, however, these data should continue to be monitored for several more years, a task which is now made straightforward because only new structures need to be added to this extensive and scrutinized list.

As mentioned above, several researchers have postulated over the years why they believe cocrystals show more or less prevalence for polymorphism than single component systems.[10,31,33] Based on our analysis herein, cocrystals appear now as the most likely crystal type to show polymorphism. To determine how this concept has changed over time, the evolution of the entries in the CSD was analyzed. One of the first publications to undertake an analysis of polymorphism in the CSD also addressed this temporal question.[22] In that article, the percentage of polymorphs compared to organics was calculated for every year from 1936-1996, albeit only for single component systems and with a slightly different set of parameters than those outlined in this study. This analysis has been extended here by looking at all polymorphs for the years 1991-2015 and by dividing the number of polymorphic entries each year by the organic entries in that year (Figure 2.3). While this does not take into account the number of unique compounds added each year like the earlier data, it does allow for better analysis of literature trends by including any structural determinations deposited in the CSD for that year that fit the outlined parameters (Tables B.7-2.13, Figures 2.4 and 2.5). The results show that throughout the years, the percentage of polymorphic entries in the CSD is constantly decreasing, most likely due to the large and increasing number of new crystal structures being deposited each year, which provides a large background effect. Sarma and Desiraju suggested that by 1996, this decrease in the percentage of polymorphs had already levelled off;[22] however it appears from these extended data to still be changing. The same decreasing trend is seen when splitting the data into single

and multicomponent crystals. However, when looking at specific types of multicomponent crystals, the results show some variance. For hydrates, the percentage of polymorphs is consistently lower than for all other crystal types, which matches with the above analysis of polymorph occurrence based on crystal types. For cocrystals however, the percentage of polymorphs has been consistent in the last 20 years, with ~4% of the entries being polymorphic. This is reflective of an increase in research activity with regards to cocrystal polymorphism, which is likely a result of the rapidly growing field of cocrystallization in general. These data stand out from all other crystal types, and further exemplifies why breakdown of polymorphic trends by crystal type is a necessary factor to better understand the origins of trends in the phenomenon as a whole.

2.3 Conclusions

Crystal polymorphism continues to be a very active area of solid-state chemistry research and sufficient structural data have been amassed in recent decades to discern general trends in the field. The fastest percentage growth in entries is in the area of cocrystal polymorphs whereas the related phenomenon of polymorphism in solvates/hydrates remains relatively less frequent. These results paint a picture of polymorphism as a pervasive phenomenon albeit one that influences different chemical classes at nonuniform rates. The future challenge is to take the results of this study and discern a physical basis for the differences in likelihood of isolating and structurally characterizing polymorphs of a specific crystal type. Efforts in this direction are ongoing.

2.4 Experimental Methods

CSD Searches. All CSD searches were conducted using ConQuest version 1.18. A text search for "polymorph" was conducted searching only for organic structures with 3D coordinates known.[c] Previously, van de Streek and Motherwell determined that of all polymorphic compounds in the CSD, only a few were not flagged with the "polymorph" tag and worked with the CSD to correct omissions, indicating that the keyword search should be sufficient to find polymorphic compounds.[21] The search described herein yielded 11,909 entries. While this

[c] The list of polymorphic refcodes from searching version 1.18 of Conquest provides structures deposited up until November of 2015 (11,909 entries). When searching in version 1.19 of Conquest for structures entered before the Nov. 2016 update, the list shows structures deposited up until August of 2015, but also with 192 entries updated after then (11,907 entries). Therefore, it is necessary to note which version of Conquest is used when searching for this data.

number is substantial, at least two structural forms must be known to characterize a compound as polymorphic, and therefore this number is automatically reduced at least in half. However, many compounds have multiple entries in the CSD, and therefore the number of unique refcodes, or families, may be used to determine the total number of distinct compounds present in the list. In the CSD, a refcode consists of a six letter code with the possibility of two numbers following. The entries with the same six letter code should constitute the same chemical entity, whether that is a single component, a salt, a solvate, or a cocrystal. Herein, the term cocrystal is defined as a crystal composed of two molecules that are solids at 25 °C and 1 atm in keeping with common usage.[28]

Examining the polymorph list for the number of refcode families yields 4,573 distinct chemical entities which were then further examined.[d] An aspect not previously explored by van de Streek and Motherwell was the assessment of whether compounds already flagged as polymorphs correctly belonged on this list.[21] Therefore, polymorphism is confirmed for each compound by analyzing the unit cell parameters and simulated powder X-ray diffraction patterns exported to Mercury (indicated by van de Streek and Motherwell to be the most reliable methods)[21] to confirm the existence of multiple structurally characterized forms of the same chemical entity.[e] No attempts are made to correct for temperature differences when assessing PXRD patterns, but instead, the associated publications for each deposited structure were consulted to determine the situations in which phase transitions were present due to temperature or pressure (Class B polymorphs). Figure 2.1 shows the breakdown of these results.

Table B.2 contains all refcode families from the search for "polymorph". Green cells indicate compounds which have been deemed Class A polymorphs. Pink cells indicate compounds which have been deemed Class B polymorphs. Yellow cells indicate compounds which had multiple entries listed, but did not have multiple polymorphic forms. Blue cells indicate compounds which only had one entry in the list. Orange cells indicate special cases which constitute the "other" category shown in Table B.6. Those entries which have a "-D" listed after the refcode indicate compounds which had polymorphic forms of a deuterated compound. In three cases, there were polymorphs for both the H and D forms of the compound,

[d] Some cases of conformational polymorphism, where molecules pack in almost identical unit cells but with minor differences, can be ambiguous to analyze by this method. In such cases, associated literature was consulted for comparison of multiple forms.
[e] Some of these have already been corrected in the 2016 version. The CSD has also been contacted to bring their attention to those discrepancies not already addressed.

and these are listed separately. The percentages of each group of compounds are shown in Figure 2.1.

Table B.3 contains all refcodes for compounds deemed to be polymorphic, whether Class A (green) or Class B (pink). The crystal types are listed for each compound. The percentages of each type of crystal for each class are shown in Figure 2.1. Refcodes with an asterisk indicate those which had only one entry flagged as polymorphs (blue in Table B.2) but were determined to be polymorphic compounds having two forms with 3D coordinates determined.

Entries in Table B.4 are not included in the overall list of polymorphs. The 60 entries in blue in Table B.2 that were determined to be polymorphic compounds are not included in Table B.4, and were instead integrated into Table B.3 and highlighted with an asterisk. Table B.3 only includes compounds that have two structurally characterized entries in a refcode which contain 3D coordinates. Several entries in Table B.4 have two forms listed as polymorphs, but do not have multiple forms with 3D coordinates known, and therefore are not included in Table B.3. In this table, PT means phase transition.

Crystal Growth & Design Searches. Crystal Growth & Design has been published since 2001. For polymorphism articles, a search was conducted for that term for the publication range of each year, and with the restriction to use print publication date (instead of web publication date). Only research articles and rapid communications were considered for this data (reviews, editorials, and perspectives were not included). The total number of articles each year was determined by counting the number of research articles and rapid communications published in each issue, in each year.

Details of Other Category. Entries in Table B.6 are in the Other category from the list of 11,909 entries flagged as polymorphs in the 2015 CSD. There are several reasons why refcodes have been included on this list. For some, two forms were observed due to replacement of hydrogen with deuterium. If the ability to hydrogen bond is removed or altered in any way, it could affect the crystal packing, and this would not fall under the category of polymorphs due to a chemical difference in the structures.[34] Some molecules were listed as a cocrystal in one structure and a salt in another, indicating those two forms would not be polymorphs but instead different compounds. Some structures were disputed between authors as to the classification of the forms as polymorphs. Most of these refcodes needed to be doubled checked in literature to

confirm polymorphism, but were not available due to deposition in the CSD as a private communication, giving no experimental data to confirm multiple forms.

Details of Polymorphism Tree Searching (Figure 2.2). Searches of the CSD[11] detailed below were conducted with ConQuest version 1.18 with the restrictions of 3D coordinates known and organics only.

Single components:

A search was conducted restricting to one chemical unit under Z/Density, and restricting entries to those not containing the name 'hydrate' or the name 'solvate'. This gives entries that should contain one neutral molecular unit (223,483 hits).

Multicomponent systems:

The search for salts involved analysis of any entry that contained two or more chemical units under Z/Density, giving 93,927 hits. Adding 'no ions' to this search resulted in 47,754, indicating that 46,173 hits contained charged species and were considered salts for this case.

The search for hydrates involved entries containing 'hydrate' in the name or a drawing of H-O-H to account for cases when water was not explicitly named as a hydrate (26,949 hits).

A simple search for solvates involved a text search for the word 'solvate' which gave 31,948 hits. However, solvates can also be listed under the term clathrate, a term used to designate host guest compounds, but the guest can be a solid or liquid. For this purpose, only clathrates that contain liquids are included. A listing of entries with the term clathrate that are not already in the solvate list produces 5,444 hits. These are analyzed to remove solid guests and 3,117 solvates were determined. Added with those in the search for just solvate, the total is 35,065.

To determine cocrystals, several searches were conducted:

A search for 2 chemical units with no ions, no hydrates, and no solvates would be two neutral components (11,314 hits). Not every one of these entries shows cocrystals; however, as some were clathrates or unlisted solvates, this list needed to be individually sorted through to find the number of cocrystal entries in this group (7,080 hits). A search for 3 or more chemical units could contain cocrystals plus a solvent, or two solvents and one neutral molecule, as well as

salts and/or ionic cocrystals. This search gave 25,667 hits and these were individually analyzed to find entries containing at least two neutral components that are solids at room temperature (5,712 hits). Added together, this results in 12,792 cocrystal entries.

Families in each category were determined by finding the number of unique refcodes in each list.

The number of polymorph entries were determined by adding a text search for "polymorph" to any of the crystal type searches outlined above.

The number of polymorph families were determined by finding the number of unique refcodes in each polymorph entries list.

The number of polymorphic compounds are the numbers determined from the outlined searches above, with the data presented in Table B.3. Breakdowns for each multicomponent crystal type also come from the data in Table B.3, and show the combination multicomponent systems (such as cocrystal salts or hydrate solvates, for example) in each crystal type.

2.5 Figures

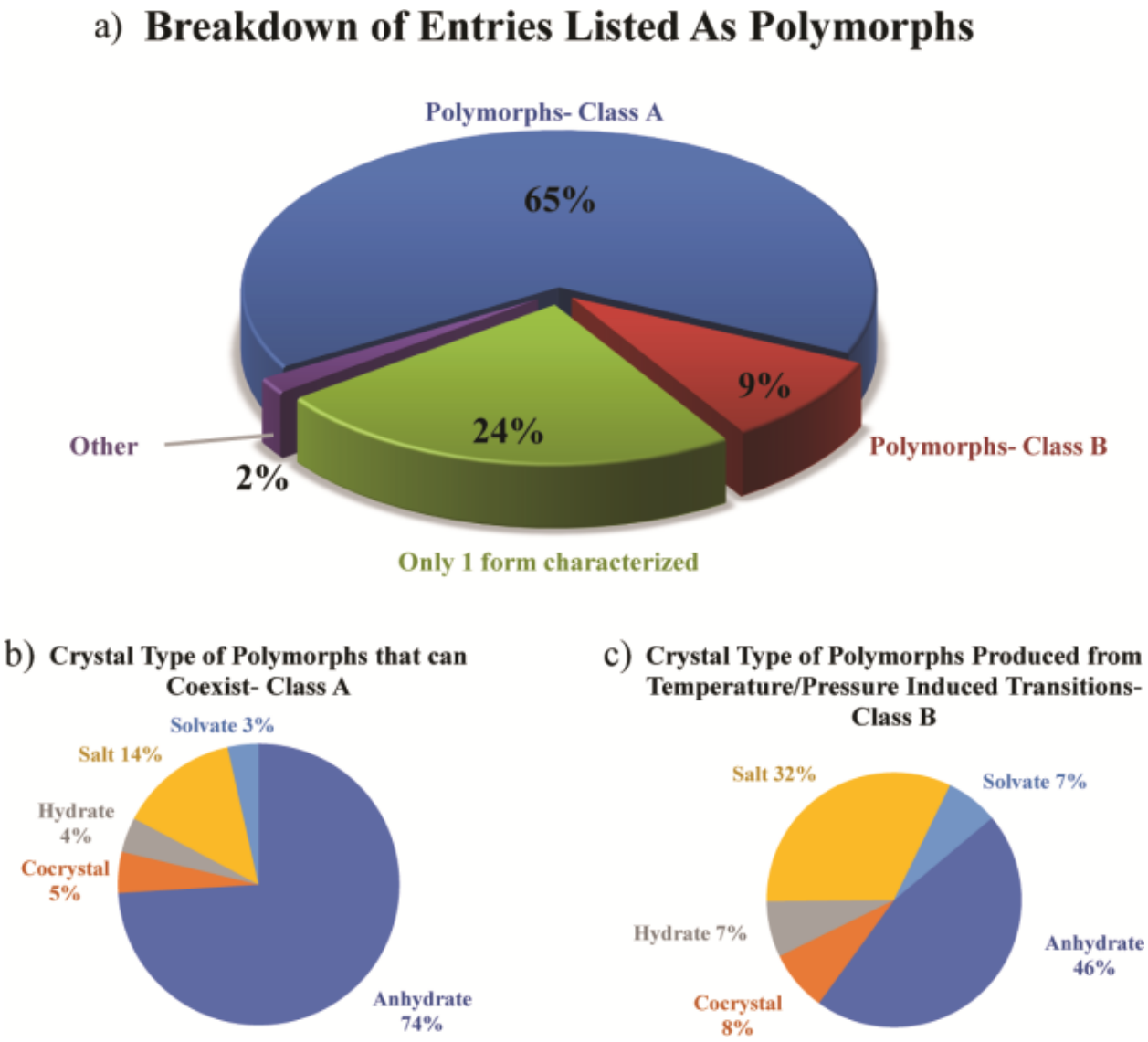

Figure 2.1. (a) Graphical breakdown of the entries flagged as polymorphs in the CSD. Further breakdown of the crystal types (anhydrates, non-hydrated solvate, salt, hydrate, and cocrystal) for (b) polymorphs that can coexist and (c) polymorphs with known phase transitions.

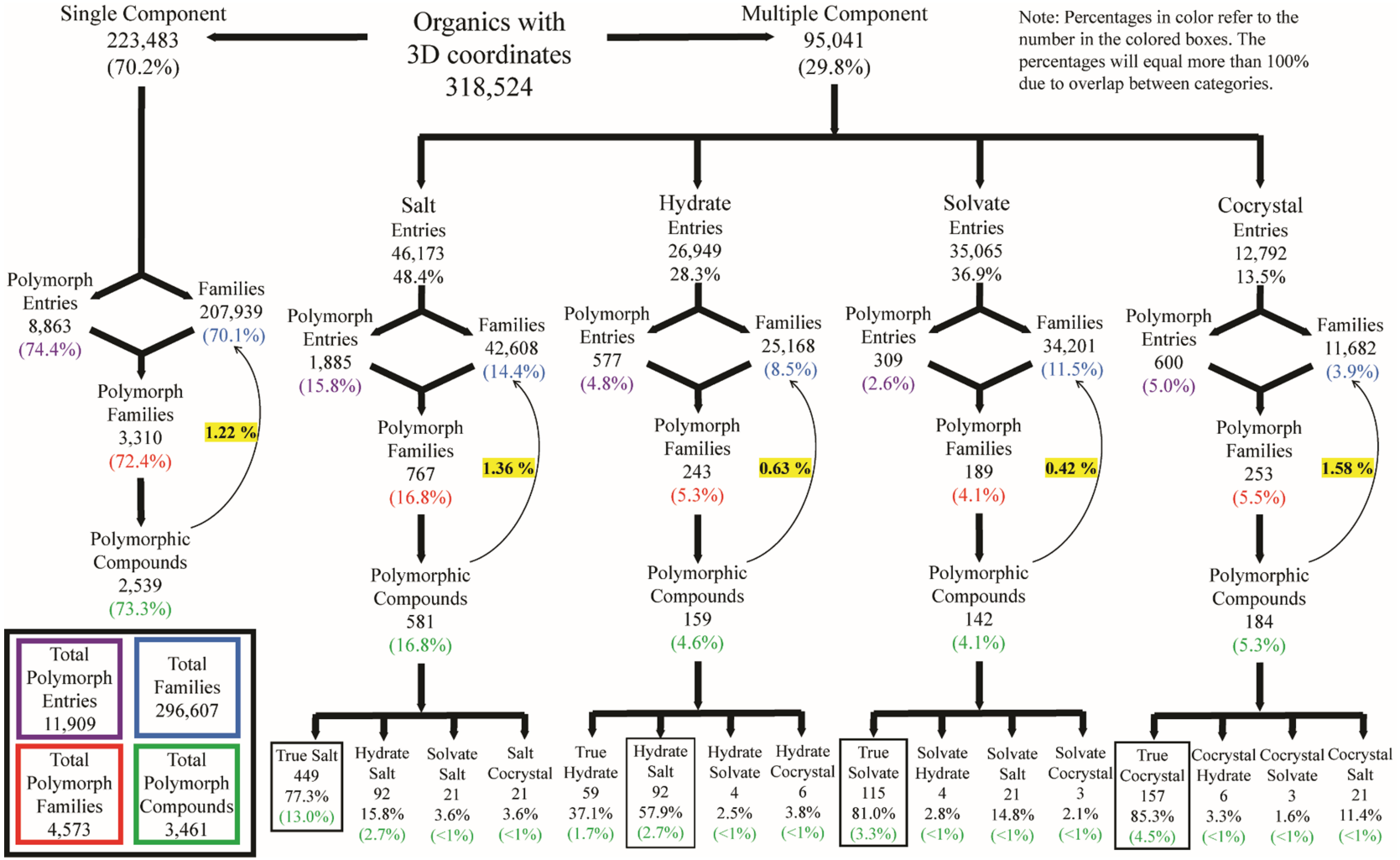

Figure 2.2. Breakdown of each type of organic crystal found in the 2015 CSD (Nov. 2015, V 5.37 with 1 update). Entries are determined from a search for that particular crystal type. Families are calculated based on the number of distinct refcode families within a particular search. Solvates in this case refer to non-hydrated solvates. True crystals refer to compounds with only the minimal chemical units necessary to produce that crystal type.[29] Polymorphic compounds are those on the list of polymorph families which have two structurally determined forms (see Experimental Methods for more details).

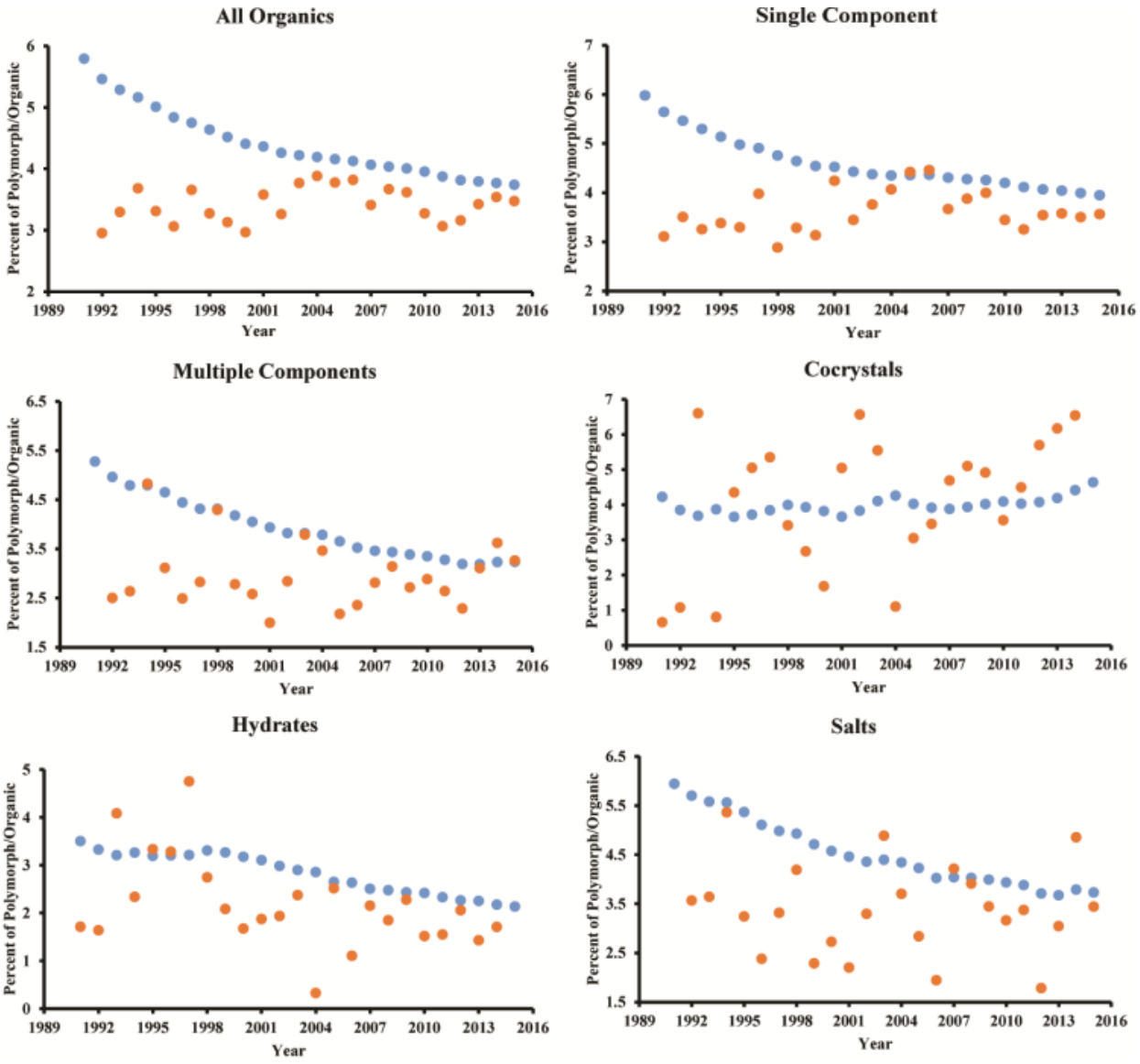

Figure 2.3. Percentage of polymorphs versus organics in the CSD according to year for specific crystal types. Blue markers refer to the total number of polymorph entries/the total number of organic entries up until that time. Orange markers refer to the number of polymorph entries/the number of organic entries for that year only.

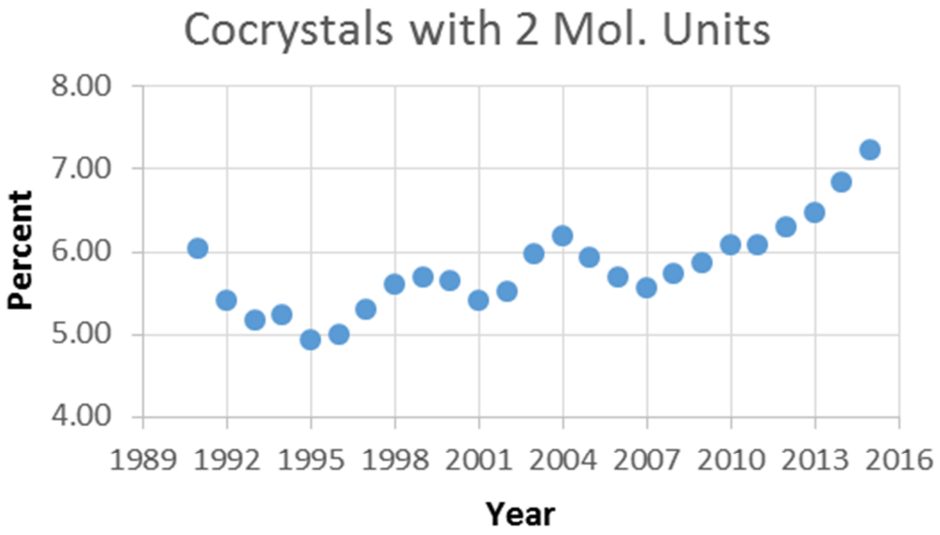

Figure 2.4. Percentage of polymorphs versus organics in the CSD for cocrystals with only 2 molecular units.

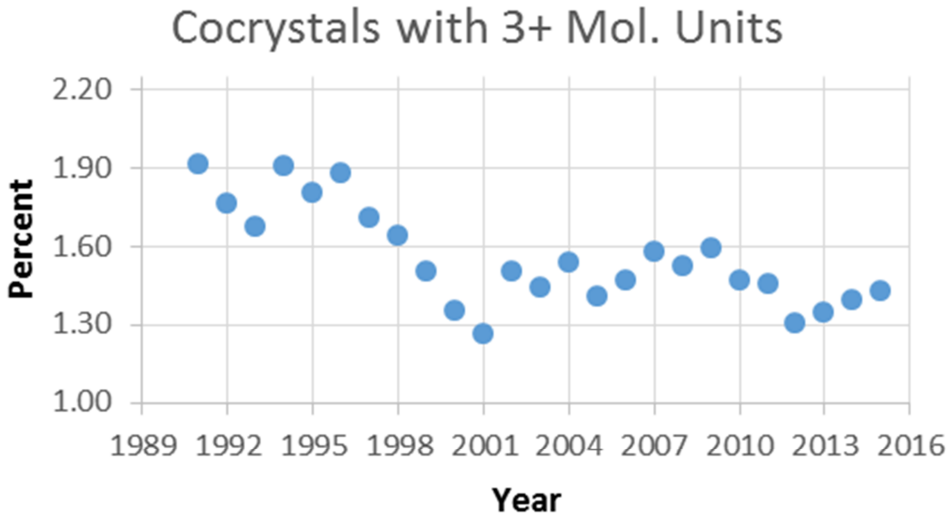

Figure 2.5. Percentage of polymorphs versus organics in the CSD for cocrystals with 3+ molecular units.

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